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(54) Title: DRUGS FOR SEX DYSFUNCTIONS

(57) Abstract: Use in sex dysfunctions of one or more of the following classes of drugs selected from the following: B) Salified and not salified, nitric oxide-donor drugs, of formula $A\text{-}X_1\text{-}N(O)_Z$, C) Organic or inorganic salts of compounds inhibiting phosphodiesterases.

DRUGS FOR SEX DYSFUNCTIONS

* * * * *

The present invention relates to drugs to be utilized for systemic and topical use in the sex dysfunction therapy, specifically in the male impotence and in female sex dysfunctions.

All over the world there is a progressive ageing of the population. It is expected that in about 5 years 17% of the population is over sixty-five. This phenomenon involves important consequences not only from a sociological point of view, but also from an epidemiological point of view. If at the beginning of the century the diseases having a greater impact on mortality and morbidity were the infectious ones, now other kinds of diseases have a greater importance. Among these, sex dysfunctions in both sexes are to be considered, which affect a very significant percentage of the population, especially due to the progressive ageing.

The male impotence or erectile dysfunction is a diffused disease. In the United States it is estimated that the impotence regards from 10 to 20 millions people over 18 years and that in the male population over forty the impotence reaches a percentage of 52%. Analogously, also a very high percentage of women (up to 76%) suffers from sex dysfunctions. For both pathologies sildenafil citrate is commonly used even though with not completely satisfactory results. The sildenafil citrate is an active drug by os exerting a beneficial vasoactive action in the male sex district. The main problem connected to the administration of this drug resides in the impossibility to dissociate its efficacy from the toxic effects, since sildenafil citrate acts strengthening the effects induced by a high production of nitric oxide, (J. Urol. 1998, 160, 257-61) and under these conditions it causes significant toxic effects. Indeed the drug is badly tolerated in patients subjected to therapy with nitrate drugs and it causes cephalea in more than 16% of the cases, so that the use is contraindicated in these therapeutic treatments. The drug is badly tolerated even when it is taken by patients affected by pathologies characterized by a high endogenous

hyperproduction of nitric oxide, such as for example cardiomyopathies (J. Am. Coll. Cardiol. 29, 716-24, 1997), infarct (Am. J. Hypertens. 1, 174-182 1999), cardiac decompensation. It is indeed known that the Sildenafil citrate has caused serious, even lethal, side effects in cardiopathic patients (Am. J. Cardiol. 84/5B, 11N-17N, 1999).

From the patent application WO 99/67231 the relaxing effect on the cavernous artery and on the cavernous body (vasodilator effect at a peripheric level) of the sildenafil nitrate salt and of the native sildenafil (citrate salt) is known. In the pharmacological experiment described in said application no information is given on the vascular tolerability of the compound in patients affected by various pathologies, for example cardiovascular pathologies. Indeed the vascular tolerability is a critical aspect if one considers that the medical speciality on the market which contains the sildenafil citrate salt is contraindicated, as above said, in cardiopathic patients.

The need was felt to have available drugs for sex dysfunctions not showing the aforesaid side effects of the citrate sildenafil.

The Applicant has unexpectedly and surprisingly found compounds able to solve this technical problem.

An object of the present invention is the systemic use, in particular oral and sublingual use, for the treatment of sex dysfunctions of one or more of the following classes of drugs:

A) organic or inorganic compounds or salts thereof, having general formula:

$$A - X_1 - N(O)_z$$

as defined hereinunder,

C) Nitrate salts of compounds able to inhibit phosphodiesterases;

in the compounds of general formula:

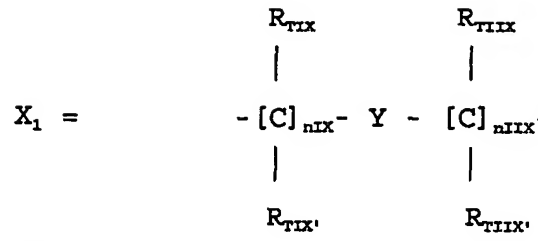
$$A - X_1 - N(O)_z$$

z is an integer and it is 1 or 2, preferably 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1-C_{10} alkyl;

X_1 is the following bivalent linking group:



$$X_1 = -[C]_{nIX}-\underset{\displaystyle R_{TIX'}}{\underset{|}{}}-Y-\underset{\displaystyle R_{TIIX}}{\underset{|}{}}-[C]_{nIIX}-O- \qquad (B)$$

wherein:

nIX is an integer in the range 0-3 , preferably 1;

nIIX is an integer in the range 1-3, preferably 1;

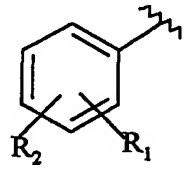
R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H;

Y is a heterocyclic ring containing one or two nitrogen atoms, optionally one oxygen or sulphur atom, said saturated, unsaturated or aromatic ring, having 5 or 6 atoms.

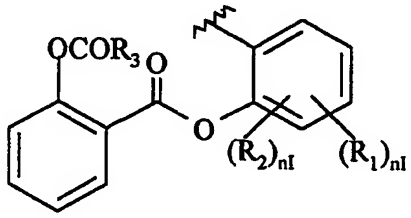
R is selected from the following groups:

Group I) wherein t = 1 and u = 1

Ia)



Ib)



wherein:

R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl, or the residue of a heterocycle with only one ring having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, linear or branched when possible C_1-C_4 alkyl; a linear or branched when possible C_1-C_4 alkoxy; a linear or branched when possible C_1-C_4

perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di-(C_{1-4}) alkylamino;

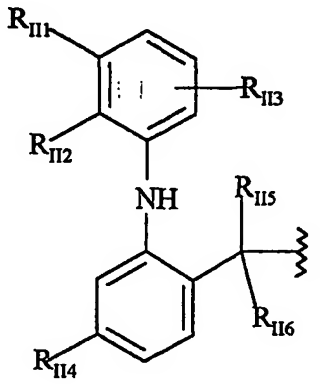
nI is an integer 0 or 1;

preferably in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho position with respect to -CO-, R_2 is hydrogen; preferably X_1 is the linking group (B) wherein $R_{IIX} = R_{IIX'} = R_{IIIX} = R_{IIIX'} = H$, $n_{II} = n_{III} = 1$;

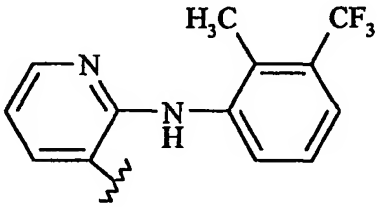
Preferably in the compounds of formula Ib) $R_3 = CH_3$, nI = 0, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;

Group II, wherein t = 1, u = 1

IIa)



IIb)



wherein:

R_{II5} is H, linear or branched when possible C_1-C_3 alkyl;

R_{II6} has the same meaning as R_{II5}, or when R_{II5} is H it can be benzyl;

R_{II1}, R_{II2} and R_{II3} can independently be hydrogen, linear or branched when possible C_1-C_6 alkyl, or linear or branched when possible C_1-C_6 alkoxy, or Cl, F, Br;

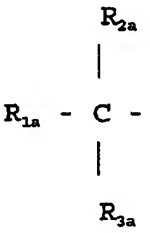
R_{II4} is R_{II1} or bromine;

the compounds wherein R_{II1}, R_{II4} are hydrogen and R_{II2} and R_{II3} are chlorine in ortho position with respect to NH are preferred;

R_{IIS} and R_{II6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);

IIb) is the residue of the 2-[(2-methyl-3-(trifluoromethyl) phenyl]amino]-3-pyridincarboxylic] acid and when the -COOH group is present the compound is known as flunixin;

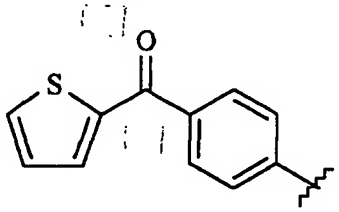
Group III) wherein t = 1, u = 1 and R is



wherein:

R_{2a} and R_{3a} are H, linear or branched when possible, substituted or not, C_1-C_{12} alkyl or allyl, with the proviso that if one of the two is allyl, the other is H; preferably R_{2a} is H, C_1-C_4 alkyl, R_{3a} is H;

R_{1a} is selected from



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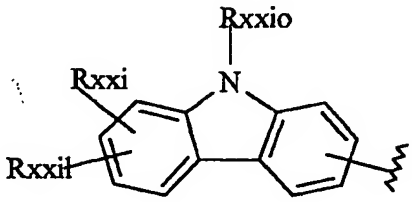

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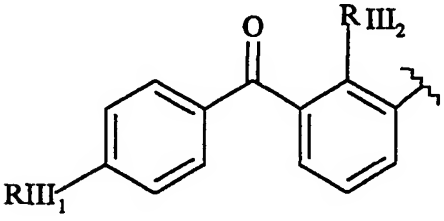

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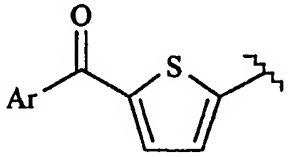

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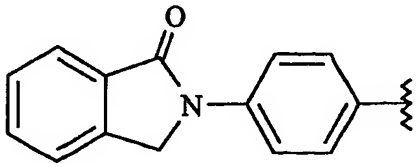

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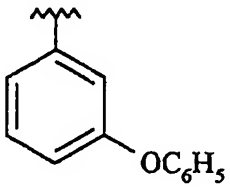

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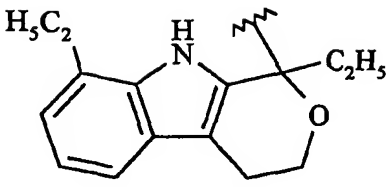
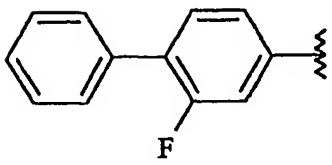


(VIII)



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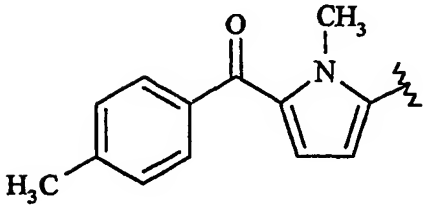
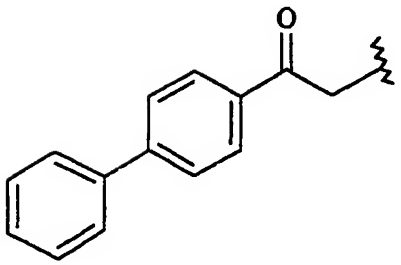
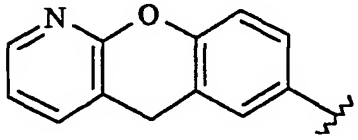


(X)

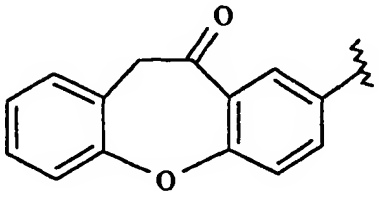


(III)

IIID) R_{1a} corresponds to the following formulas:



(IIIa)



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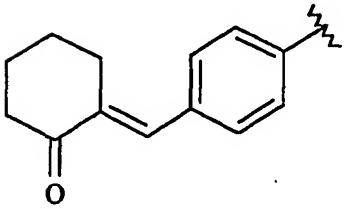
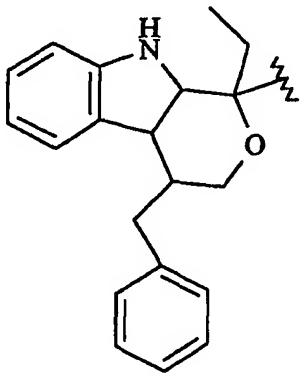


(XXXI)



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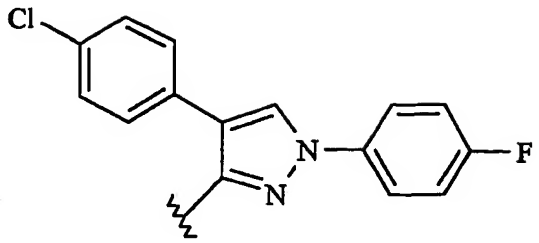

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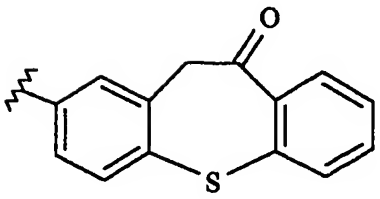

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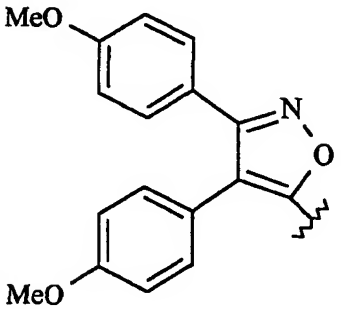

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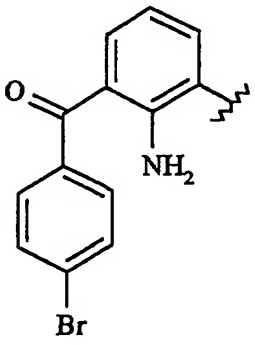


(XII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue:
  R_{III1} is H, SR_{III3} wherein R_{III3} contains from 1 to 4 carbon atoms, linear or branched when possible;
  R_{III2} is H, hydroxy;
  the compounds wherein R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O, are preferred;
- when R_{1a} is as adefined in formula (XXI), carprofen residue:
  R_{xxio} is H, linear or branched when possible alkyl from 1 to 6 carbon atoms, C_1-C_6 alkoxycarbonyl linked to a C_1-C_6 alkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;
  R_{xxi} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} wherein R_{xxi2} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2,

amino; sulphamoyl, di-alkyl sulphamoyl with C_1-C_6 alkyl, or difluoroalkylsulphonyl with C_1-C_3 alkyl;

R_{xxi1} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{III3} being R_{III3} as above defined, C_1-C_3 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2, amino, mono- or di-alkyl-amino C_1-C_6; sulphamoyl, di-alkyl sulphamoyl C_1-C_6, or di-fluoroalkylsulphamoyl as above defined; or R_{xxi} together with R_{xxi1} is a C_1-C_6 alkylen dioxy;

the compounds are preferred wherein R_{xxio} is H, the linking group is in position 2, R_{xxi} is H, R_{xxi1} is chlorine and is in para position with respect to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;

- when R_{1a} is as defined in formula (XXXV), tiaprofenic acid residue:

  Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, alkanoyl and alkoxy C_1-C_6, C_1-C_6 preferably C_1C_3 . trialkyl, cyclopentyl, cyclohexyl, cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

  the preferred compounds of (XXXV) are those wherein Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O;
- when R_{1a} is as defined in formula (II), suprofen residue, of which the preferred one has been indicated, wherein R_{3a} is H, R_{2a} is methyl and X = O, as described and obtained in USP 4,035,376 herein incorporated by reference;
- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when R_{2a} = H and R_{3a} = CH_3; of indobufen when R_{2a} is equal to H and R_{3a} = C_2H_5; X = O, as described and obtained according to USP 3,997,669 herein incorported by reference;
- when R_{1a} is as defined in formula (VIII), R is the etodolac residue when R_{2a} = R_{3a} = H and X = O, as described and obtained according to USP 3,843,681 herein incorporated by reference;
- when R_{1a} is as defined in formula (VII), R is the fenoprofen residue when R_{3a} = H, R_{2a} = CH_3 and X = O, as described and obtained according to USP 3,600,437 herein incorporated by reference;

- when R_{1a} is as defined in formula (III), R is the fenbufen residue when R_{2a} = R_{3a} = H and X = O, as described and obtained according to USP 3,784,701 herein incorporated by reference;
- when R_{1a} is as defined in formula (IX), R is the flurbiprofen residue when R_{3a} = H, R_{2a} = CH_3, X = O;
- when R_{1a} is as defined in formula (X) R is the tolmetin residue when R_{2a} = R_{3a} = H, X = O, as described and obtained according to FR 1,574,570 herein incorporated by reference;

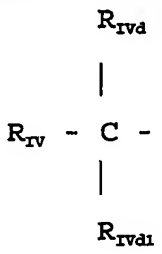
In group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when R_{2a} = H and R_{3a} = CH_3 the pranoprofen residue is obtained: α-methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid; the preferred compound has R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O:
- (XXX), when R_{2a} = H and R_{3a} = CH_3, the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid; the preferred compound has R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O.
- (XXXI), when R_{2a} = H and R_{3a} = CH_3, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexyliden methyl) phenyl]propionic acid; the preferred compound has R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- (XXXII), when R_{2a} = R_{3a} = H, the Pemedolac residue is obtained; the preferred compound has R_{2a} = R_{3a} = H, u = 1 and X = O;
- (XXXIII), when R_{2a} = R_{3a} = H, the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolic acid derivatives;
  The preferred compounds have R_{2a} = R_{3a} = H, u = 1 and X = O;
- (XXXVI), when R_{2a} = H, R_{3a} = CH_3, the zaltoprofen residue is obtained; when the residue is saturated with a hydroxyl or amino group, or with the carboxylic function the compounds are known as dibenzothiepine derivatives; the preferred compounds have R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- (XXXVII), when R_{2a} = R_{3a} = H the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid

when the residue is CH_2-COOH; the preferred compounds have R_{2a} = R_{3a} = H, t = 1 and X = O;

- (XII), when R_{2a} = R_{3a} = H the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid; the preferred compounds have u = 1, t = 1, X = O, R_{2a} = R_{3a} = H; or t = 0;

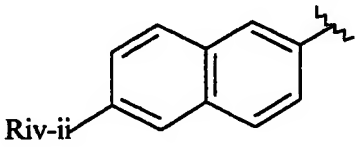
in group IV) wherein t = 1, u = 1, R is



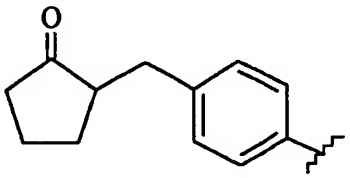
wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched when possible C_1 - C_6, preferably C_1 and C_2 alkyl, or difluoroalkyl with the alkyl from 1 to 6 carbon atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

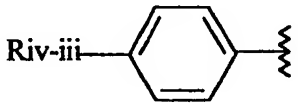
R_{IV} has the following meaning:



(II)



(X)



(III)

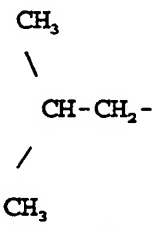
wherein the compounds of group IV) have the following meanings:

- in formula (II)

R_{iv-ii} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_7 alkoxymethyl, C_1-C_3 trifluoroalkyl, vinyl, ethynyl, halogen, C_1-C_6 alkoxy, difluoroalkoxy, with C_1-C_7 alkyl, C_1-C_7 alkoxy-methyloxy, alkylthiomethyloxy with C_1-C_7 alkyl, alkyl methylthio with C_1-C_7 alkyl, cyan, difluoromethylthio,

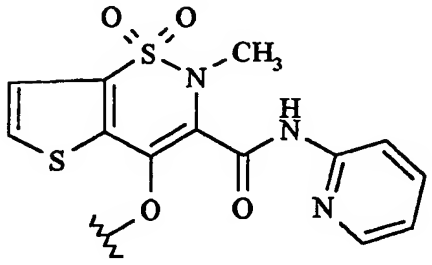
phenyl- or phenylalkyl substituted with C_1-C_8 alkyl; preferably $R_{iv\text{-}ii}$ is CH_3O-, R_{ivd} is H and R_{ivd1} is CH_3, and it is known as naproxen residue;
X = O and X_1 is as above defined for Ia);

- in formula (X), of which the loxoprofen residue, described in USP 4,161,538 herein incorporated by reference, has been indicated, the compounds wherein R_{ivd} is H and R_{ivd1} is CH_3, X = O and X_1 is as above defined for Ia) are preferred;
- in formula (III):
$R_{iv\text{-}iii}$ is a C_2-C_5 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 carbon atoms, optionally substituted in position 1 by a C_1-C_2 alkyl;
it is preferred the compound wherein $R_{iv\text{-}iii}$ is

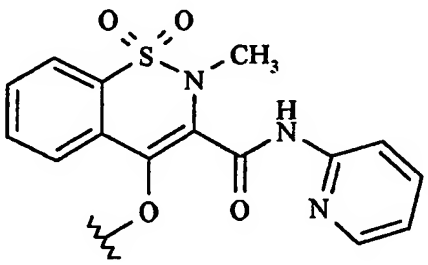


and R_{ivd} = H, R_{ivd1} is CH_3, compound known as ibuprofen residue; X = O and X_1 is as above defined for Ia);

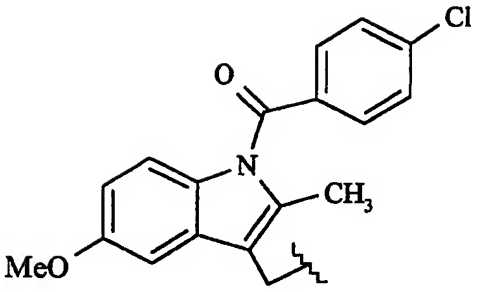
Group V)



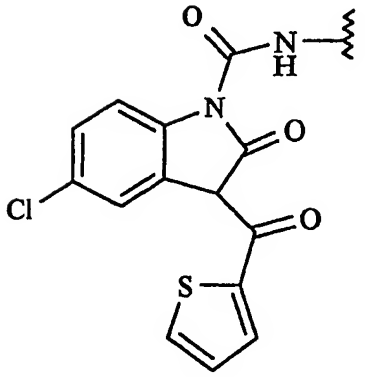
(VII)



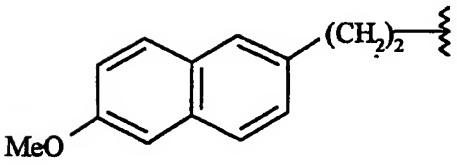
(IX)



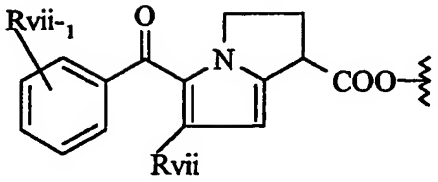
(IV)



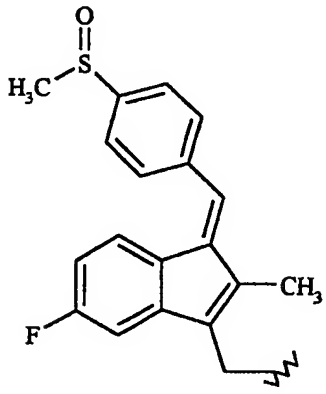
(V)



(III)

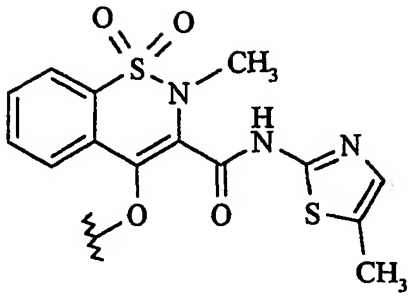


(II)

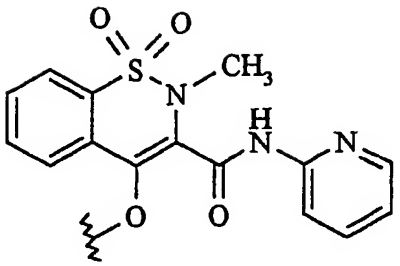


(LX)

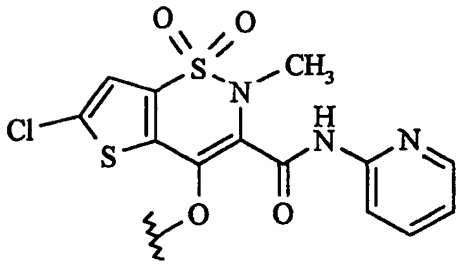
Group VE)



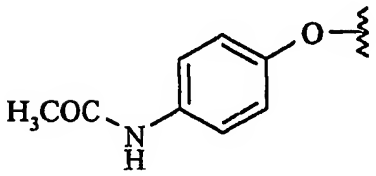
(X)



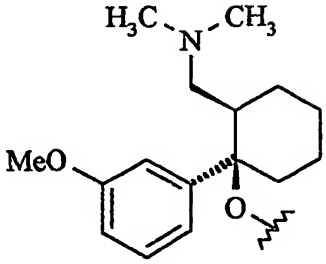
(XI)



(XIII)



(XXXX)



(XXXXI)

in group V), the compounds have the following meanings:

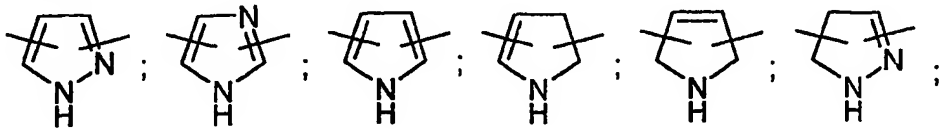
- when R is formula (II),
  R_{vii} is H or a linear or branched when possible C_1-C_4 alkyl;
  R_{vii-1} is R_{vii}, or a linear or branched when possible C_1-C_4 alkoxy; Cl, F, Br; the position of R_{vii-1} being ortho, or meta, or para;
  the residue of the known Ketorolac is preferred, wherein R_{vii} and R_{vii-1} are H, and A = R (A being the group of the formula $A\text{-}X_1\text{-}NO_2$) and t = 0;
- when R is formula (V),
  of which the residue of the known tenidap has been indicated, as described and obtained in USP 4,556,672

herein incorporated by reference;
in these compounds of formula (V) A = R and t = 0,

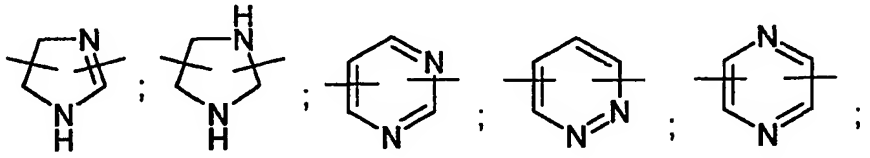
- when R is formula (VII),
  of which the residue of the known tenoxicam has been indicated, A is RCO, t = 1 u = 0 or A is R and t = 0, as described and obtained in DE 2,537,070 herein incorporated by reference;
- when R is formula (IX),
  wherein A = R and t = 0, or A = RCO with t = 1 and u = 0, the residue of the known piroxicam has been indicated, as described and obtained in USP 3,591,584 herein incorporated by reference;
- when R is formula (III)
  wherein A = RCOO, t = 1 and u = 0 or 1; or t = 0 and A = R, of which the residue of the known nabumetone has been indicated, as described and obtained in USP 4,061,779 herein incorporated by reference;
- when R is formula (IV)
  wherein A = RCOO, t = 1 and u = 1,
  of which the indomethacin residue has been indicated, as described and obtained in USP 3,161,654, herein incorporated by reference;
- when R = formula (LX) and in $(COX_u)_t$ u = t = 1 and X is oxygen, the precursor compound is known as sulindac;
- when R is formula (X), the X residue is known as meloxicam; the preferred compounds are those wherein A = RCO, t = 1 and u = 0;
- when R is formula (XI) the residue is known as ampiroxicam when the termination is $-CH(CH_3)OCOC_2H_5$; the preferred compounds have A = RCO, t = 1 and u = 0;
- when R is formula (XIII) and the valence is saturated with H, the residue derives from lornoxicam; the preferred compounds have A = RCO, t = 1 and u = 0;
- when R is formula (XXXX) and the valence is saturated with H the compound known as paracetamol is obtained, as described and obtained in USP 2,998,450 herein incorporated by reference;
- when R is formula (XXXXI) and the valence is saturated with H, the compound known as Tramadol is obtained, as described and obtained in USP 3,652,589;

the preferred compounds according to the present invention obtainable with the radicals corresponding to the formulas (XXXX) and (XXXXI) have A= RCO, t = 1 and u = 0.

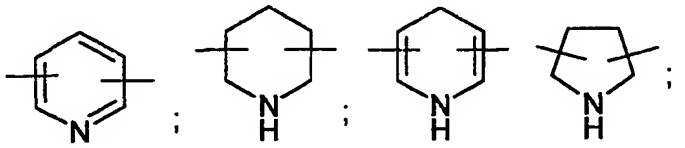
Preferably Y is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



(Y12) (Y13) (Y14) (Y15)

Preferably Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6.

The preferred of Y is Y12 (pyridyl) substituted in position 2 and 6. The bonds can be also in a non symmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) can be 3,5-disubstituted.

The X_1 precursors as defined by formula (B), wherein the free valence of the oxygen is saturated with H and the free valence of the end carbon is saturated either with a carboxylic or hydroxyl group, are commercially available compounds or they can be obtained by known methods of the prior art.

The compounds containing R of group I of the type Ia) are described in patent application WO 92/01668 wherein also

the preparation methods are mentioned. This patent is herein incorporated by reference. The compounds of type Ib) are for example prepared by using the method indicated in The Merck Index, XI ed., 1989, pag. 16, No. 95 for the acetylsalicylsalicylic acid residue. The modifications of the compounds of formula Ib) can be obtained by using the processes mentioned in patent application WO 92/01668.

The compounds wherein R is of group II) are described in patent application WO 94/04484 and USP 3,558,690 wherein also the preparation methods are indicated. These patents are herein incorporated by reference.

The starting compound of IIb), when the valence is saturated with -COOH (flunixin), is obtained according to USP 3,337,570 and USP 3,689,653, both herein incorporated by reference. The compounds containing the substituents mentioned in the previous patents are equivalent to flunixin.

The compounds wherein R is of group III) are described and obtained by the processes mentioned in the following patents:
patent application PCT/EP/93 03193; for the compounds of formula (IV) see also USP 3,641,127; for the compounds of formula (XXI) see also USP 3,896,145; for the compounds of formula (IX) flurbiprofen residue see also USP 3,755,427; for the compounds of formula (II) see also USP 4,035,376; for the compounds of formula (VI) see also USP 3,997,669; for the compounds of formula (VIII) see also USP 3,843,681; for the compound of formula (VII) see also USP 3,600,437; for the compounds of formula (III) see also USP 3,784,701. All these mentioned patents are herein incorporated by reference.

The procedures for the preparation of the compounds of class IIID) are the following:

The residue IIIa) is obtained by preparing the acid compound according to USP 3,931,205, the valence is saturated with $-CH(CH_3)-COOH$. The compounds containing the substituents mentioned in the previous patent are equivalent to pranoprofen. The residue (XXX) is prepared through the compound with the group $-CH(CH_3)-COOH$ (bermoprofen) according to USP 4,238,620 herein incorporated by reference. Other equivalent products are described in the above mentioned patent.

The residue (XXXI) is prepared by starting from the corresponding acid $-CH(CH_3)-COOH$ according to USP 4,254,274. Equivalent compounds are described in the same patent.

The residue (XXXII) is prepared according to EP 238,226 herein incorporated by reference, when the valence is saturated with $-CH_2-COOH$. Equivalent products are reported in said patents as 1,3,4,9 tetrahydropyran [3,4-b] indol-1-acetic substituted acids.

The residue (XXXIII) is prepared from pirazolac and the valence is saturated with $-CH_2-COOH$, as indicated in EP 54,812 herein incorporated by reference. Equivalent products are described in said patent.

The residue (XXXVI) is prepared according to UK 2,035,311 herein incorporated by reference, by starting from zaltoprofen and having the $-CH(CH_3)-COOH$ termination. Equivalent products are described in said patent.

The process for preparing the residue (XXXVII) is obtained by starting from mofezolac and it is prepared according to EP 26,928. Equivalent products are reported in the same patent.

The compounds wherein R is of group IV) are described in GB patent application 2,283,238, wherein also the preparation methods are indicated; this patent is herein incorporated by reference.

In group IV) the compounds can also be obtained:
for the compounds of formula (II) using USP 3,904,682; the compounds of formula (X) according to USP 4,161,538; the compounds of formula (III) according to USP 3,228,831. The herein mentioned patents are incorporated in the present application by reference.

In group V) the compounds can also be obtained: for the compounds of formula (II) using USP 4,089,969 herein incorporated by reference; the compounds of formula (V) can be obtained according to USP 4,556,672 herein incorporated by reference.

The residue (X) is prepared according to the German patent 2,756,113. Equivalent products are described in said patent.

The residue (XI) is prepared according to EP 147,177, herein incorporated by reference, starting from ampiroxicam

having the termination $-CH(CH_3)OCOOC_2H_5$. Equivalent products are described in said patent.

The residue (XII) is prepared according to J. Med. Chem., vol. 27 No. 11, Nov. 1984, Walsh et Al. "Antiinflammatory Agents. 3. Synthesis and Pharmacological Evaluation of 2-amino-3-benzoylphenylacetic Acid and Analogues", herein incorporated by reference. Equivalent products are described in said publication.

The residue (XIII) is prepared starting from lornoxicam, wherein the valence is saturated with H. It is prepared according to GB 2,003,877. Equivalent products are described in said patent.

The residue (LX) in group V is prepared from Sulindac, obtained according to US 3,654,349.

In general the connection between A and X_1 is, as seen, of ester or amidic type (NH or NR_{1c}, as defined in X) when R is of groups I, II, III, IV and V. For the formation of such connection all the synthesis routes well known for the formation of such bonds are usable.

The preparation of the compounds of formula $A-X_1-N(O)_z$ with the linking group X_1 of formula (B) is described in published PCT application WO 00/51988 in the name of the Applicant, herein incorporated by reference.

The compounds inhibiting the phosphodiesterase C) salified with nitric acid are selected from the following: (C1) 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyra-zol[4,3-d]-pyrimidin-5-yl)-phenyl]sulphoyl]-4-methyl-piperazine (Sildenafil), (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (Zaprinast), (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidine pyrimido [5,4-d]-pyrimidine (dipyridamol), (C4) 6-chloro-4-(1,3-dioxaindan-5-yl)methylamino-2(4-carboxy-1-piperidinyl)-quinazoline, (C5) N-(phenylmethyl)-1-ethyl-1H-pyrazol-[3,4-b]-quinolin-4-amine, (C6) 1-(2-chlorobenzyl)-3-isobutyryl-2-propyl-6-aminocarbonyl-indol., (C7) 1-benzyl-6-choro-2-[1-[3-(imidazol-1-yl)propyl]indol-5-yl-amino carbo-nyl]benzimidazol, (C8) 2-(1-imidazolyl)-5-(phenyl)-4-(1,3-dioxaindan-5-yl)methyl aminopyrimidine, (C9) 6-ethynyl-4-(2-metoxyethyl)amino-2-(1-imidazolyl)quinazoline, (C10) 1-cyclo-pentyl-3-ethyl-6-(2-propoxyphenyl)pyrazol[3,4-d]pyrimidin-4-one, (C11) 1-cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-pyrazol-

[3,4-d]-pyrimidin-4-one, (C12) 1,3-dimethyl-6-(2-propoxy-5-methansulphonamidophenyl)-1,5-dihydro pyrazol[3,4-d]-pyrimidin-4-one, (C13) (6R, 12aR)-2,3, 6,7,12, 12a-hexahydro-2-methyl-6-(1,3-dioxan-5-yl)pyrazin [2',1':6,1] pyrido[3,4-b]indol-1,4-dione, (C14) 1-propyl-3-methyl-6-[2-propoxy-5-[(4'-methyl-1-pyrazinyl)sulphonamido] phenyl]-1,5-dihydropyrazol[3,4-d]pyrimidin-4-one, (C15) 3-(4-amino carbonyl-1-piperidinyl)-6-cyan-8-(3-chloro-4-methoxy-phthalazine, (C16) 2-(1-imidazolyl)-4-(1,3-dioxaindan-5-yl) methylamino-7,8-dihydro-5H-thiopyran[3,2-d]pyrimidine, (C17) 1-Cyclopentyl-3-ethyl-6-(3-ethoxypyrid-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-one, (C18) 1-[3-[1-[(4-Fluorophenyl)methyl]-7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propoxyphenyl] carboxamide.

The pharmaceutical formulations usable for the specific use according to the present invention are those well known to the skilled in the art and which can be prepared according to the texts widely known in the prior art. See for exampe the volume "Remington's Pharmaceutical Sciences 15a Ed.".

The dosages of the salts of the invention in their pharmaceutical compositions are equal, and generally lower than those of their precursors of the above mentioned classes, said salts generally being more effective and better tolerated.

The salts of the compounds A) and C) can be used as such, preferably in formulations administrable according to conventional administration routes of drugs. For example they can be administered by systemic route, for example by oral, sublingual route.

Surprisingly it has been found by the Applicant that the sildenafil nitrate has a power ratio, calculated as ratio between the myorelaxing effect on the cavernous body and the systemic pressure effect (see the data on the aorta reported in Table 1), clearly in favour of the myorelaxing effect. This shows that the sildenafil nitrate can be used for the impotence treatment also by cardiopathic people since the pressure effect (aorta) is very reduced.

For patients suffering from sex dysfunctions (male and female) it has been found that the salts of compounds A) and the nitrate salts of compounds C) for systemic use have a low

pressure effect wherefore the power ratio, calculated as above, is improved with respect to the commercial sildenafil (citrate salt).

It has been unexpectedly found that the salts of the compounds of the invention can also be topically administered as such, preferably using the corresponding formulations containing them as active principles. This is a surprising fact since it is not said that a compound active by systemic route is active also by topical route. It has been unexpectedly found that also the salts of compounds C), different from nitrates, are active by topical route, as such or when administered carried in the above formulations.

Examples of organic salts of C) are oxalate, tartrate, maleate, succinate, citrate, glycinate, lysinate; examples of inorganic anions are nitrate, chloride, sulphate, phosphate.

The administration by topical route of compounds A) and of the salts of C), in particular of the phosphodiesterase inhibitors, was not predictable for the use according to the present invention, in particular for the treatment of the male impotence and of the female sex dysfunctions, since the myorelaxing action of said products is not direct but it takes place through the strengthening of the endogen mediator cGMP which is formed through the nitric oxide.

In particular, as regards the compositions for topical use, the salt amount of the compounds of classes A) and C) in the pharmaceutical form, for the predicted use according to the present invention, is in the range 0.5-10%, preferably 2-6%, as percentage by weight on the total weight of the composition. Said formulations for topical use can be in the form of salves, creams and gels and are prepared according to the techniques known to the skilled of the art, as described for example in the above mentioned volume.

The above compounds inhibiting the phosphodiesterases are synthesized as described in the following references (C1): G.B. 92480; (C2): DE 2162096; (C3): The Merck Index 12th Ed.; (C4):WO 9422855; (C5): WO 9628159; (C6): WO 9632379; (C7): WO 9703070; (C8): USP 5,525,604; (C9): USP 5,436,233; (C10): WO 9628448; (C11): WO 9628429; (C12): EP 636626; (C13): WO 9519978; (C14): EP 636626; (C15): WO 9605176; (C16): EP

728759; (C17): US 5,294,612; (C18): J. Med. Chem. 2000, 43, 1257-1263.

Constitutes a further object of the present invention nitrooxy derivatives of the following phosphodiesterase inhibitors:

- (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (zaprinast),
- (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidine pyrimido [5,4-d]-pyrimidine (dipyridamol),
- (C4) 6-chloro-4-(1,3-dioxaindan-5-yl)methylamino-2(4-carboxy-1-piperidinyl)-quinazoline,

of formula:

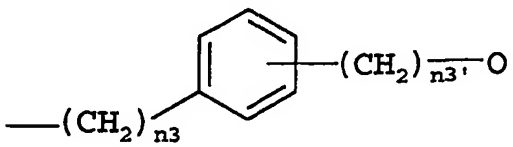
$$A - X_{1A} - N(O)_z \quad (IC)$$

Wherein A is as above defined, and

- in the case of (C2) t = 0 and R is the phenyloxy radical derived by substituting the ether group on the phenyl ring of Zaprinast with an hydroxy function (see Tetrahedron letters 1967 pages 4131 and following ones, Tetrahedron letters 1968 24 pages 2289 and following ones);
- in the case of (C3) t = 0 and R is the alcoxy radical derived from the precursor;
- in the case of (C4) t = u = 1 and X is oxygen;

X_{1A} can have the meaning of X_1 above and also the following ones:

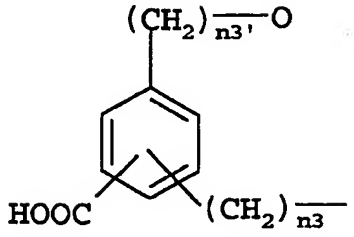
- an alkylene group R' wherein R' is a C_1-C_{20} linear or branched when possible, preferably having from 2 to 6 carbon atoms, optionally substituted with one or more of the following groups: $-NHCOR_3$, wherein R_3 is C_1-C_4 linear or branched alkyl, $-NH_2$, or OH
- a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with side chain R', R' being as above, one or more carbon atoms of the cycloalkylene ring can optionally be substituted by heteroatoms;
-



(IIIAr)

wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

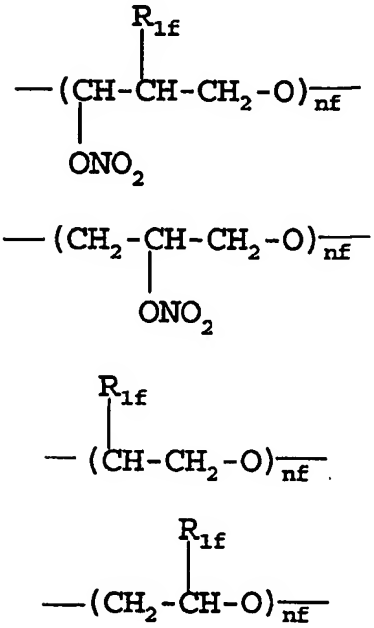
-



(IVAr)

wherein n3 and n3' have the above meaning;

-



wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6, preferably from 1 to 4.

The compounds of formula (IC) as above defined can be prepared with known methods; when the bivalent linking bridge is of formula (B), the same methods above described apply. When the linking bridge have the other meanings the methods described in WO 95/30641.

The nitrate salts of the phosphodiesterase inhibitors can be prepared by known methods, for example as described in the patent application WO 99/67231; the other salts of compounds C) with anions different from nitrate are prepared by known methods of the prior art, such as for example described in patent application WO 96/28448.

The following Examples illustrate the invention but they do not limit the scope thereof.

EXAMPLE 1

Preparation of a formulation for topical use containing as active principle the 2(acetyloxy)benzoic acid 6-(nitroxymethyl)-2-methylpyridyl ester hydrochloride (NCX 4050).

The compound is prepared according to Example 1 of patent application PCT/EP 00/01454.

Components of the formulation for topical use:

NCX 4050	4.2 g
white vaseline	24 g
cetostearyl alcohol	9.5 g
polyoxyethylene (60 OE) sorbitan monostearate (Polysorbate® 60)	4.8 g
glycerine	9.5 g
purified water	48 g
total	100 g

Preparation of the formulation

In a weighed vessel the white vaseline (24 g) and the cetostearyl alcohol (9.5 g) are melted. To the melted mass (70°C) a solution previously obtained by dissolving NCX 4050 (4.2 g), polysorbate® 60 (4.8 g) and glycerine (9.5 g) in fresh-boiled purified water is added under stirring. At the end of the addition one continues to stir until complete cooling of the mass and at last it is determined by weighing the evaporated water amount, which is added to the formulation until obtaining the required total weight (100 g).

PHARMACOLOGICAL EXAMPLES

EXAMPLE F1

The relaxing effect of the tested drugs on carvernous body tissues has been evaluated with experiments in vitro as a measure of the inhibiting action on the impotence, and on aorta tissues as expression of the undesired hypotensive effect.

Preparation of tissues

White New Zealand rabbits were sacrificed, cavernous body and aorta specimens were taken and suitably prepared for the determination of the myorelaxing activity in vitro, according to the procedure described by J. Jeremy (Br. J. Urology 79,958-63,1997).

The tissues were precontracted with phenylephrine (10 μM) and the relaxation was determined in the presence of the compounds object of the invention.

The compounds examined in this test are reported in Table 1. The 2-(acetyloxy)benzoic acid 6-(nitroxy methyl)-2-methylpyridyl ester hydrochloride (NCX 4050) is prepared as described in patent application PCT/EP 00/01454 (Ex. 1), the sildenafil nitrate has been prepared as described in patent application WO 99/67231 (Ex. 3). The products used in the experiment were dissolved in dimethylsulphoxide, except sodium nitroprussiate which was dissolved in distilled water.

The data of the Table show that the products of the invention are more effective than the reference substances in relaxing the cavernous body, and induce a lower vasorelaxing effect on the aorta.

EXAMPLE F2

The effect of the sildenafil citrate and sildenafil nitrate on the aorta relaxation was evaluated with an experiment in vitro in the presence of a conventional NO-donor (sodium nitroprussiate). Under these conditions it is known that the sildenafil citrate causes hypotension.

The experiment was carried out as described in the previous Example, by using aorta tissues taken from white New Zealand rabbits. The tissue strips are treated first with sodium nitroprussiate 10^{-7} M, then a part of the strips was treated with sildenafil citrate 10^{-7} M and another part with sildenafil nitrate 10^{-7} M.

The results of the experiment are reported in Table 2 and are expressed as percentage of the aorta relaxation with respect to the initial treatment with sodium nitroprussiate and they show that the sildenafil nitrate causes a lower strengthening of the relaxing effect induced by sodium nitroprussiate compared with the sildenafil citrate. Therefore the sildenafil nitrate is less hypotensive than the sildenafil citrate.

Table 1

Experiment in vitro on the myorelaxing effect of the cavernous body and of aorta of the following compounds NCX 4050, sildenafil nitrate, sildenafil citrate and sodium nitroprussiate as a comparison.

Treatment	Concentration (M)	Cavernous body % relaxation	Aorta %	Power ratio
NCX 4050	10-6	80	80	1
Sodium Nitroprussiate	10-6	50	100	0.5
Sildenafil Nitrate	10-6	100	20	5
Sildenafil Citrate	3x 10-5	50	75	0.66

Table 2

Experiment in vitro on the myorelaxing effect on aorta tissues pretreated with sodium nitroprussiate and then treated, respectively, with sildenafil nitrate and sildenafil citrate		
Treatment	Concentration (M)	Aorta relaxation %
Sodium Nitroprussiate	10^{-7}	100
Sildenafil Nitrate	10^{-7}	120
Sildenafil Citrate	10^{-7}	170

CLAIMS

1. Use for the treatment of sex dysfunctions of one or more of the following classes of drugs:

A) salified and non salified nitric oxide donor drugs, of formula

$$A - X_1 - N(O)_z$$

wherein the meaning of the terms appearing in the formula is as defined hereunder;

C) nitrate salts of compounds inhibiting phospho-diesterases;

in the compounds of general formula:

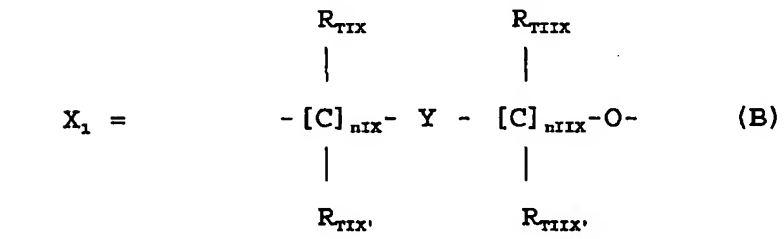
$$A - X_1 - N(O)_z$$

z is an integer and is 1 or 2, preferably 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1-C_{10} alkyl;

X_1 is the following bivalent linking group:



(B)

wherein:

nIX is an integer in the range 0-3;

nIIX is an integer in the range 1-3;

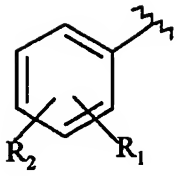
R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl;

Y is an heterocyclic ring containing one or two nitrogen atoms, optionally one oxygen or sulphur atom, said saturated, unsaturated or aromatic ring having 5 or 6 atoms;

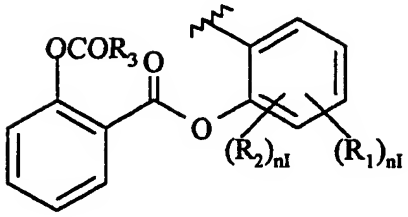
R of the radical A of formula $A - X_1 - N(O)_z$ is selected from the following groups:

Group I) wherein t = 1 and u = 1

Ia)



Ib)



wherein:

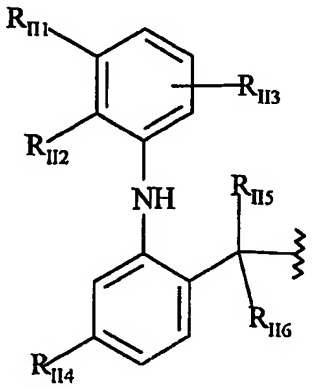
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or a linear or branched C_3-C_5 alkyl, or the residue of an heterocycle having only one ring having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more hetero-atoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, linear or branched C_1-C_4 alkyl, linear or branched C_1-C_4 alkoxy; a linear or branched C_1-C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di-(C_{1-4}) alkylamino;

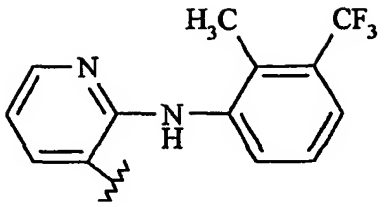
nI is an integer 0 or 1;

group II) wherein t = 1, u = 1

IIa)



IIb)



wherein:

R_{II5} is H, linear or branched when possible C_1-C_3 alkyl;

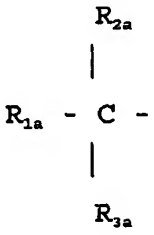
R_{II6} has the same meaning as R_{II5}, or when R_{II5} is H it can be benzyl;

R_{II1}, R_{II2} and R_{II3} can independently be hydrogen, linear or branched when possible C_1-C_6 alkyl, or linear or branched when possible C_1-C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{II1} or bromine;

IIb) is the residue of the 2-[(2-methyl-3-(trifluoromethyl)phenyl]amino]-3-pyridincarboxylic] acid and when the -COOH group is present it is known as flunixin;

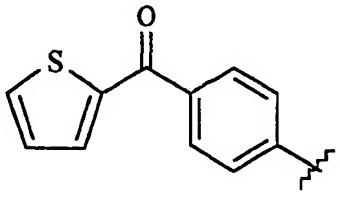
group III) wherein t = 1, u = 1 and R is



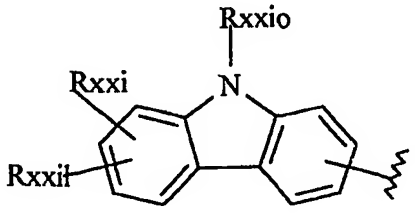
wherein:

R_{2a} and R_{3a} are H, linear or branched when possible, substituted or not, C_1-C_{12} alkyl or allyl, with the proviso that if one of the two is allyl the other is H; preferably R_{2a} is H, C_1-C_4 alkyl, R_{3a} is H;

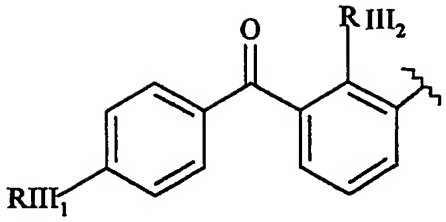
R_{1a} is selected from



(II)



(XXI)



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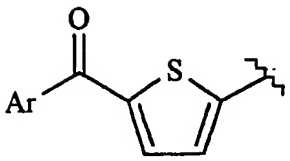
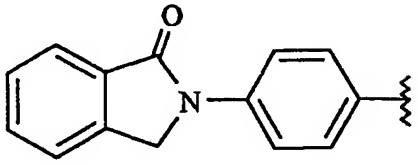
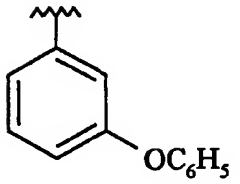


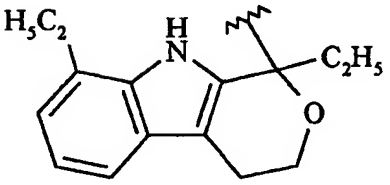
(XXXV)



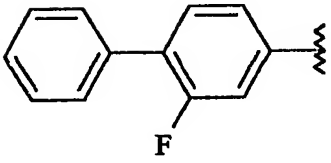
(VI)



(VII)



(VIII)



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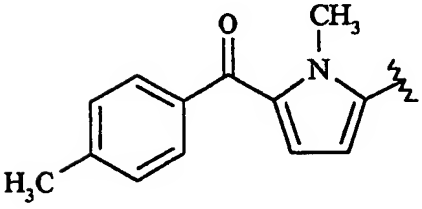
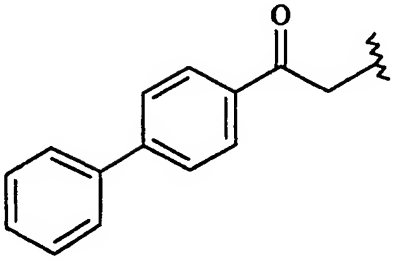
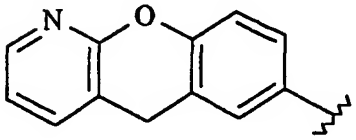


(X)

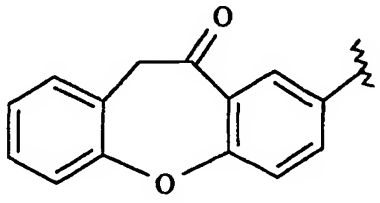


(III)

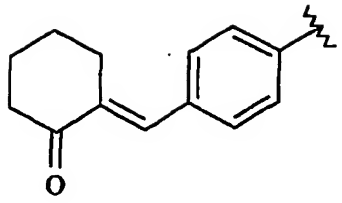
IIID) R_{1a} corresponds to the following formulas:



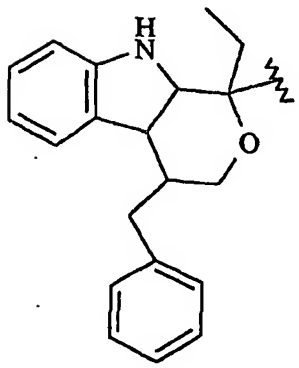
(IIIa)



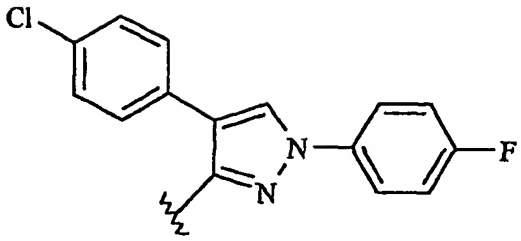
(XXX)



(XXXI)



(XXXII)



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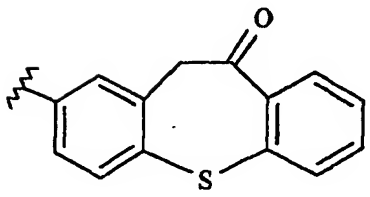
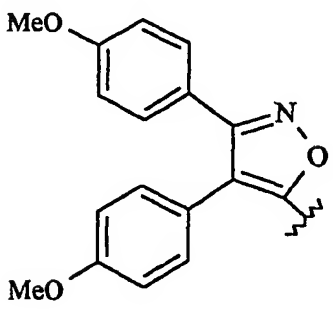
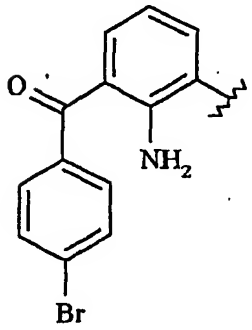


(XXXVI)



(XXXVII)



(XII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue: R_{III1} is H, SR_{III3} wherein R_{III3} contains from 1 to 4 carbon atoms, linear or branched when possible; R_{III2} is H, hydroxy;
- when R_{1a} is as defined in formula (XXI), carprofen residue: R_{xxio} is H, linear or branched when possible alkyl from 1 to 6 carbon atoms, C_1-C_6 alkoxycarbonyl linked to a C_1-C_6 alkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkanoyl, optionally substituted

with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xxi} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} wherein R_{xxi2} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2, amino; sulphamoyl, di-alkyl sulphamoyl with C_1-C_6 alkyl or difluoroalkyl-sulphonyl with C_1-C_3 alkyl;

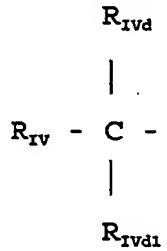
R_{xxi1} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{III3} being R_{III3} as above defined, C_1-C_3 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2, amino, mono- or di-alkyl-amino C_1-C_6; sulphamoyl, di-alkyl sulphamoyl C_1-C_6, or di-fluoroalkylsulphamoyl as above defined; or R_{xxi} together with R_{xxi1} is an alkylen dioxy C_1-C_6;

- when R_{1a} is as defined in formula (XXXV) tiaprofenic acid residue:
  Ar is phenyl, hydroxyphenyl optionally mono or polysubstituted with halogen, alkanoyl and alkoxy C_1-C_6, trialkyl C_1-C_6, preferably C_1-C_3, cyclopentyl, cyclohexyl, cycloheptyl, heteroaryl, preferably tienyl, furyl optionally containing OH, pyridyl;
- when R_{1a} is as defined in formula (II), suprofen residue, wherein R_{3a} is H, R_{2a} is methyl and X = O;
- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when R_{2a} = H and R_{3a} = CH_3; of indobufen when R_{2a} is equal to H and R_{3a} = C_2H_5; X = O;
- when R_{1a} is as defined in formula (VIII), R is the etodolac residue when R_{2a} = R_{3a} = H and X = O;
- when R_{1a} is as defined in formula (VII), R is the fenoprofen residue when R_{3a} = H, R_{2a} = CH_3 and X = O;
- when R_{1a} is as defined in formula (III), R is the fenbufen residue when R_{2a} = R_{3a} = H and X = O;
- when R_{1a} is as defined in formula (IX), R is the flurbiprofen residue when R_{3a} = H, R_{2a} = CH_3, X = O;
- when R_{1a} is as defined in formula (X) R is the tolmetin residue when R_{2a} = R_{3a} = H, X = O;

in group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when R_{2a} = H and R_{3a} = CH_3 the pranoprofen residue is obtained: α-methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid; the preferred compound has R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O:
- (XXX), when R_{2a} = H and R_{3a} = CH_3 the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid;
- (XXXI), when R_{2a} = H and R_{3a} = CH_3, R is the radical of the CS-670 compound: 2-[4-(2-oxo-1-cyclo-hexyliden methyl) phenyl]propionic acid;
- (XXXII), when R_{2a} = R_{3a} = H the Pemedolac residue is obtained;
- (XXXIII), when R_{2a} = R_{3a} = H the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluoro phe-nyl)-3-pyrazolic acid;
- (XXXVI), when R_{2a} = H, R_{3a} = CH_3 the zaltoprofen residue is obtained; when the residue is saturated with an hydroxyl or amino group, or with the carboxylic function the compounds are known as dibenzothiepine derivatives;
- (XXXVII), when R_{2a} = R_{3a} = H the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-ace-tic acid;
- (XII), when R_{2a} = R_{3a} = H the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid;

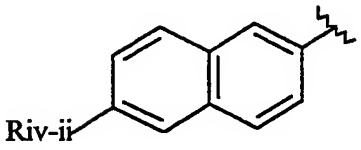
in group IV) wherein t = 1, u = 1, R is



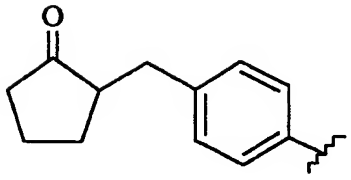
wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched C_1-C_6, preferably C_1 and C_2 alkyl, or difluo-roalkyl with the alkyl from 1 to 6 carbon atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

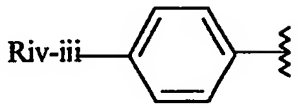
R_{IV} has the following meaning:



(II)



(X)

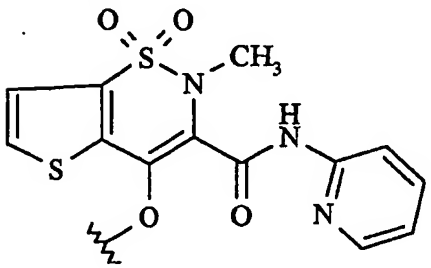


(III)

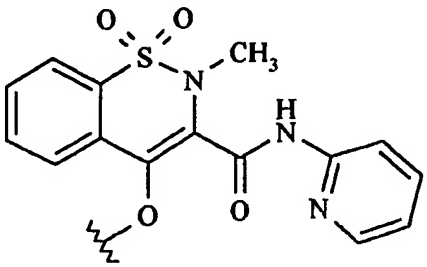
wherein the compounds of group IV) have the following meanings:

- in formula (II):
  R_{iv-ii} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_7 alkoxy-methyl, C_1-C_3 trifluoroalkyl, vinyl, ethynyl, halogen, C_1-C_6 alkoxy, difluoroalkoxy, with C_1-C_7 alkyl, C_1-C_7 alkoxymethyloxy, alkylthio methyloxy with C_1-C_7 alkyl, alkyl methylthio with C_1-C_7 alkyl, cyano, difluoromethylthio, phenyl- or phenylalkyl substituted with C_1-C_8 alkyl.
- formula (X) loxoprofen residue;
- in formula (III):
  R_{iv-iii} is a C_2-C_5 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 carbon atoms, optionally substituted in position 1 by a C_1-C_2 alkyl;

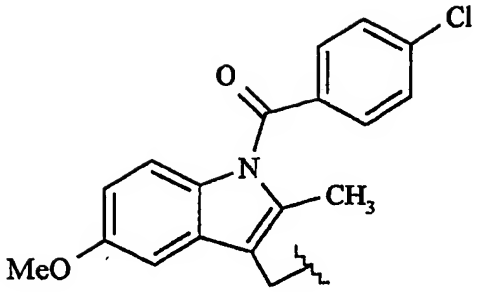
Group V)



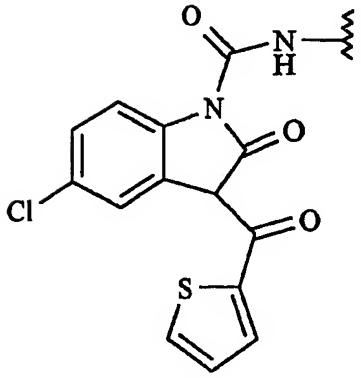
(VII)



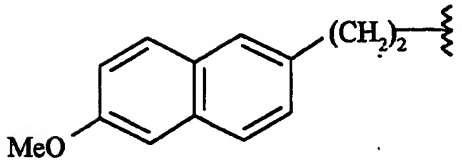
(IX)



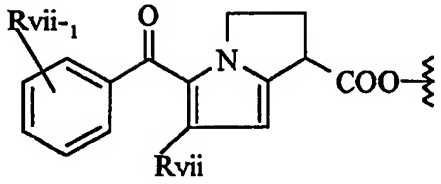
(IV)



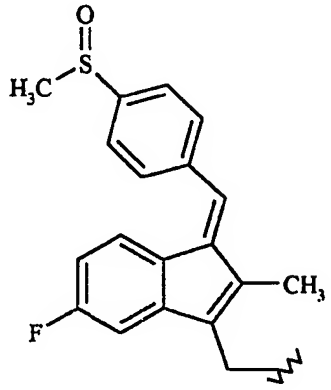
(V)



(III)

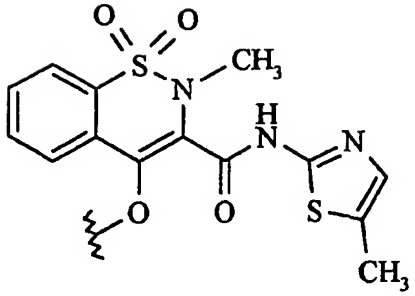


(II)

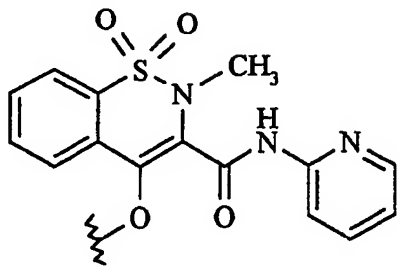


(LX)

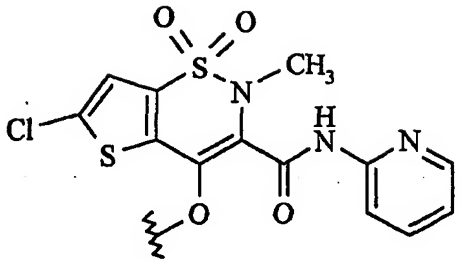
Group VE)



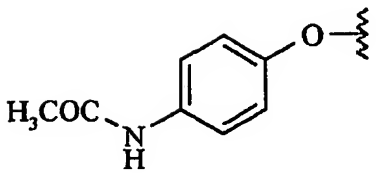
(X)



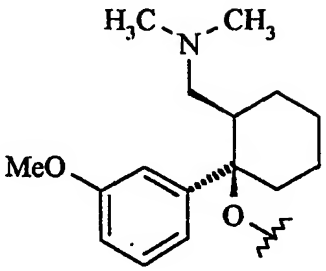
(XI)



(XIII)



(XXXX)



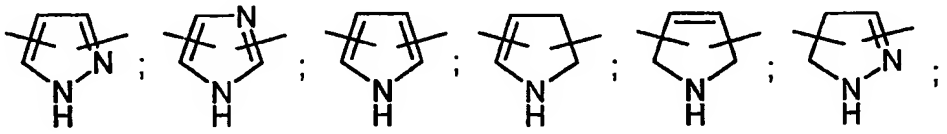
(XXXXI)

In group V):

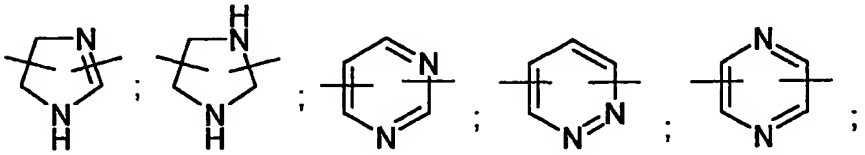
- when R is formula (II), R_{vii} is H or a linear or branched C_1-C_4 alkyl;
  R_{vii-1} is R_{vii}, or a linear or branched C_1-C_4 alkoxy; Cl, F, Br; the position of R_{vii-1} being ortho, or metha, or para;
- when R is formula (V),
  of which the residue of the known tenidap has been indicated;
- When R is formula (V) A = R and t = 0,
- when R is formula (VII), A is RCO, t = 1 u = 0 or A is R and t = 0;
- when R is formula (IX), A = R and t = 0, or A = RCO with t = 1 and u = 0;
- when R is formula (III) A = RCOO, t = 1 and u = 0 or 1; or t = 0 and A = R;
- when R is formula (IV) A = RCOO, t = 1 and u = 1;
- when R is formula (LX) and in $(COX_u)_t$ u = t = 1 and X is oxygen, the precursor compound is sulindac;
- when R is formula (X) it is the meloxicam residue;
- when R is formula (XI) the residue is known as ampiroxicam when the termination is $-CH(CH_3)OCOC_2H_5$;

- when R is formula (XIII) and the valence is saturated with H, the residue derives from lornoxicam;
- when R is formula (XXXX) and the valence is saturated with H the compound is known as paracetamol;
- when R is formula (XXXXI) and the valence is saturated with H the compound is known as tramadol.

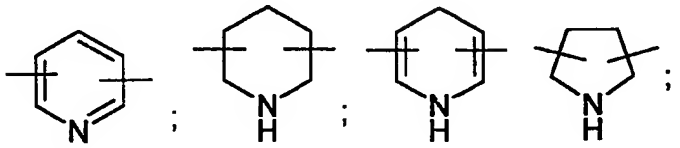
2. Use according to claim 1, wherein Y is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



(Y12) (Y13) (Y14) (Y15)

3. Use according to claim 2, wherein Y is Y12 (pyridyl) substituted in position 2 and 6.

4. Use according to claims 1-3, wherein in the compounds A) of formula A-X_1-N(O)$_z$ z is 2 and nIX and nIIX in formula (B) of X_1 are integers equal to 1 and R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are equal to H.

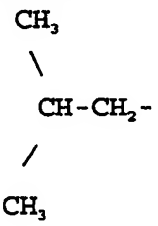
5. Use according to claims 1-4, wherein in the compounds of formula A) A-X_1-N(O)$_z$ R, X, u and t of formula A = R(COX$_u$)$_t$, and Y in formula (B) of X_1, take the following meanings:

- when R is selected from the group I), in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho position with respect to -CO-, R_2 is hydrogen; in X_1 R_{IIX} = $R_{IIX'}$ = R_{IIIX} = $R_{IIIX'}$ = H,
  n_{IX} = n_{IIX} = 1 and Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6; in the compounds of formula Ib) R_3 = CH_3, nI = 0, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;
- when R is selected in group II) in formula IIa R_{II1}, R_{II4} are hydrogen and R_{II2} and R_{II3} are chlorine in ortho position with respect to NH; R_{II5} and R_{II6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);
- when R is selected in group III),
- when R_{1a} is as defined in formula (IV) R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;
- when R_{1a} is as defined in formula (XXI) R_{xxio} is H, the linking group is in position 2, R_{xxi} is H, R_{xxi1} is chlorine and it is in para position with respect to nitrogen;
- when R_{1a} is as defined in formula (XXXV) Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O; R_{3a} is H, R_{2a} is methyl and X is O;
- when R_{1a} is as defined in formula IIIa), R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXX) R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXI), R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXII), R_{2a} = R_{3a} = H, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXIII), R_{2a} = R_{3a} = H, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXVI), R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXVII), R_{2a} = R_{3a} = H, t = 1 and X = O;

- when R_{1a} is as defined in formula (XII), R_{2a} = R_{3a} = H, u = 1, t = 1, X = O, R_{2a} = R_{3a} = H; or t = 0;

when R is selected in group IV),

- when R_{IV} is formula (II), R_{iv-ii} = CH_3O-, R_{IVd} = H and R_{IVd1} = CH_3, X = O and X_1 is as above defined for Ia);
- when R_{IV} is formula (X), R_{IVd} = H, R_{IVd1} = CH_3, X = O and X_1 is as above defined for Ia);
- when R_{IV} is formula (III), R_{iv-iii} is



and R_{IVd} = H, R_{IVd1} is CH_3, X = O and X_1 is as above defined for Ia);

when R is selected in group V,

- when R is formula (II), R_{vii} and R_{vii-1} are H, and A = R;
- when R is formula (X), A = RCO, t = 1 and u = 0;
- when R is formula (XI), A = RCO, t = 1 and u = 0;
- when R is formula (XIII), A = RCO, t = 1 and u = 0;
- when R corresponds to formula (XXXX) or (XXXXI), A= RCO, t = 1 and u = 0.

Use according to claims 1-5, wherein the nitrate salts of the compounds inhibiting the phosphodiesterase are selected from the following: (C1) 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyra-zol[4,3-d]-pyrimidin-5-yl)-phenyl]sulphoyl]-4-methyl-piperazine (Sildena-fil), (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (Zapri-nast), (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidine py-rimido [5,4-d]-pyrimidine (dipyridamol), (C4) 6-chloro-4-(1,3-dioxaindan-5-yl)methylamino-2(4-carboxy-1-pyperidi-nyl)-quinazoline, (C5) N-(phenyl methyl)-1-ethyl-1H-pyra-zol-[3,4-b]-quinolin-4-amine, (C6) 1-(2-chlorobenzyl)-3-isobutyryl-2-propyl-6-amino carbonyl-indol, (C7) 1-benzyl-6-chloro-2-[1-[3-(imidazol-1-yl)propyl]indol-5-yl-amino carbonyl] benzimidazol, (C8) 2-(1-imidazolyl)-5-(phenyl)-4-(1,3-dioxaindan-5-yl)methyl

aminopyrimidine, (C9) 6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazo-line, (C10) 1-cyclopentyl-3-ethyl-6-(2-propoxyphenyl)py-razol[3,4-d]pyrimidin-4-one, (C11) 1-cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-pyrazol-[3,4-d]-pyrimidin-4-one, (C12) 1,3-dimethyl-6-(2-propoxy-5-methansulphonamidophe-nyl)-1,5-dihydro pyrazol[3,4-d]-pyrimidin-4-one, (C13) (6R, 12aR)-2,3, 6,7,12, 12a-hexahydro-2-methyl-6-(1,3-dioxan-5-yl)pyrazine [2',1':6,1] pyrido[3,4-b]indol-1,4-dione, (C14) 1-propyl-3-methyl-6-[2-propoxy-5-[(4'-me-thyl-1-pyrazinyl)sul-phonamido] phenyl]-1,5-dihydropyra-zol[3,4-d]pyrimidin-4-one, (C15) 3-(4-amino carbonyl-1-piperidinyl)-6-cyan-8-(3-chloro-4-methoxy-phthalazine, (C16) 2-(1-imidazolyl)-4-(1,3-dioxaindan-5-yl) methyla-mino-7,8-dihydro-5H-thio-pyran[3,2-d]pyrimidine, (C17) 1-Cyclopentyl-3-ethyl-6-(3-ethoxypyrid-4-yl)-1H-pyrazolo [3,4-d]pyrimidin-4-one, (C18) 1-[3-[1-[(4-Fluorophenyl) methyl]-7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propoxyphenyl] carboxamide.

7. Use according to claims 1-6, obtained by the pharmaceutical formulations containing one or more salts of classes A) and C).
8. Use according to claim 7, wherein said formulaions are administrable by oral and sublingual route.
9. Use according to claims 1-7 wherein said formulations are for topical use and comprise as active principles also the salts of compounds C) different from nitrates.
10. Use according to claim 9, wherein the organic anions of said salts of compounds C) different from nitrates are selected from oxalate, tartrate, maleate, succinate, citrate, glycinate, lysinate; and the inorganic ones are selected from chloride, sulphate, phosphate.
11. Use according to claims 9-10, wherein the formulations for topical use comprise an active principle amount in the range 0.5 and 10% by weight.

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(74) Agents: **SAMA, Daniele** et al.; Sama Patents, Via G.B. Morgagni 2, I-20129 Milano (IT).

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— *with international search report*

(88) Date of publication of the international search report:
5 December 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/011707 A3

(54) Title: DRUGS FOR INCONTINENCE

(57) Abstract: Use in the incontinence of one or more of the following classes of drugs selected from the following: B) salified and non salified nitric oxide-donor drugs, of formula: A - X_1 - $N(O)_z$, B') nitrate salts of drugs used for the incontinence, and which do not contain in the molecule a nitric oxide donor group; C) organic or inorganic salts of compounds inhibiting phosphodiesterases.

INTERNATIONAL SEARCH REPORT

Int ial Application No
PCT/EP 01/08734

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/04 A61P13/00 A61K31/216 A61K31/416 A61K31/472
A61K31/137 A61K31/4409 A61K31/352 A61K31/44 A61K31/519
A61K31/453 A61K31/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 09948 A (NICOX SA ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 12 March 1998 (1998-03-12) cited in the application * see in particular p. 45, l. 10 - p. 47, l. 7; claim 1 *	12,14,15
X	WO 96 37202 A (ALZA CORP) 28 November 1996 (1996-11-28) * see in particular p. 3, l. 22-24; p. 5, l. 8-11; claim 2 *	12,14,15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2002	02.09.02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rodriguez-Palmero, M

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INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/EP 01/08734

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	LINDSTROM, LEIF H.: "Effect of pilocarpine and oxotremorine on hormone-activated copulatory behavior in the ovariectomized hamster" NAUNYN-SCHMIEDEBERG'S ARCH. PHARMACOL. (1972), 275(3), 233-41 , XP001055429 * see in particular p. 235, first paragraph; p. 239, first paragraph of the discussion *	12,14,15
E	WO 01 89473 A (SCHLYTER JIMMY HIRSCHSPRUNG ;SCHULTZ ANN CHRISTINA (DK); SUNDGREEN) 29 November 2001 (2001-11-29) * see in particular claims 6 and 59 *	12,14,15
P,X	US 6 203 817 B1 (JOHNSON JUANITA A ET AL) 20 March 2001 (2001-03-20) * see in particular column 14, table 4; column 15, table 5 *	12,14,15
X	WO 99 67231 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 29 December 1999 (1999-12-29) * see in particular p. 2, l. 23 - p. 3, l. 5; p. 12, l. 11 and 12; p. 18, l. 18-21; p. 29, example 3; p. 33, example 10; p. 44, examples 16 and 17; claims 3, 4 and 6 *	12,14,15
X	GB 2 330 579 A (GHARDA CHEMICALS LIMITED) 28 April 1999 (1999-04-28) * see in particular claim 4 *	12,14
P,X	EP 1 092 719 A (PFIZER LTD ;PFIZER (US)) 18 April 2001 (2001-04-18) * see in particular p. 2, paragraph 1; p. 3, paragraphs 6 and 7; p. 12, paragraph 41 *	13-15
X	DE 195 40 642 A (STIEF CHRISTIAN GEORG PRIV DOZ) 7 May 1997 (1997-05-07) * see in particular column 2, l. 23 - column 3, l. 29; claims *	14
X	EP 1 020 190 A (PFIZER PROD INC) 19 July 2000 (2000-07-19) * see in particular p. 2, paragraph 3; p. 3, paragraph 10 and 15; p. 4, paragraph 16; p. 9, paragraph 43; claims 21, 24 and 25 *	14
X	US 5 525 604 A (LEE SUNG J ET AL) 11 June 1996 (1996-06-11) * see in particular column 44, example 1(bb) *	14

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INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/EP 01/08734

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 436 233 A (LEE SUNG J ET AL) 25 July 1995 (1995-07-25) * see in particular column 18, table 1 and column 80, example 18 *	14
X	WO 96 28448 A (SANOFI WINTHROP INC) 19 September 1996 (1996-09-19) * see in particular p. 12, l. 4-35; p. 17, example 6 *	14
X	EP 0 943 613 A (KYOWA HAKKO KOGYO KK) 22 September 1999 (1999-09-22) * see in particular p. 3, paragraph 1; p. 5, paragraph 22 *	13
P,X	WO 00 51988 A (NICOX SA ;DEL SOLDATO PIERO (IT); BENEDINI FRANCESCA (IT)) 8 September 2000 (2000-09-08) * see in particular examples 1-8, 13 and 14 *	14
A	SULLIVAN J ET AL: "Pharmacological management of incontinence." EUROPEAN UROLOGY, vol. 36, no. SUPPL. 1, June 1999 (1999-06), pages 89-95, XP001094443 Pre-Congress Satellite Symposium on a1-Adrenoceptors as Targets for Therapeutic Agents in Urology in connection with the XIIIth Congress of Pharmacology;Paris, France; Munich, Germany; July 23-24, 1998; July 26, 1998 ISSN: 0302-2838 * see in particular p. 89, right column, 3rd paragraph; p. 92, left column, 2nd last paragraph *	12-15

INTERNATIONAL SEARCH REPORT

.....national application No.
PCT/EP 01/08734

Box I Observati ns where ertain claims were f und un archable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-11
because they relate to subject matter not required to be searched by this Authority, namely:

The present claims 1-11 concern subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT and have therefore not been searched.

2. [X] Claims Nos.: 12-15 (all of them partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claim : 12; 14 and 15 (partially)

   Nitrate salts of drugs used for the incontinence and which do not contain in the molecule a nitric oxide donor group, formulations containing them and their use as a medicament.

2. Claim : 13; 14 and 15 (partially)

   Organic or inorganic salts of compounds inhibiting phosphodiesterases, formulations containing them and their use as a medicament.

3. Claim : 14 (partially)

   Formulations containing nitric oxide donor drugs, salified and non salified of formula A-X1-N(O)z as defined in claim 1 of the present application.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 12-15 (all of them partially)

Present claims 12-15, as far as they depend on claims 1 and 6, relate to an extremely large number of possible compounds or formulations. The term "drugs used for the incontinence" used in claim 1 encompasses an unlimited group of compounds, which is permanently changing, so that a complete search is impossible. In fact, the claims contain so many options that a lack of conciseness within the meaning of Article 6 PCT arises. The same reasoning applies mutatis mutandis for the functional terms used in claim 6 for the groups B'1-B'9 and B'11 and in claim 1 for group C. Consequently, the search of claims 12-15 has been carried out for those parts of the application which do appear to be concise, namely for the concrete compounds mentioned in claims 6 (group B'10), 7 and 8.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/EP 01/08734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9809948 A	12-03-1998	IT MI961821 A1	04-03-1998
		AU 729533 B2	01-02-2001
		AU 4301097 A	26-03-1998
		BR 9712008 A	24-08-1999
		CN 1234792 A	10-11-1999
		WO 9809948 A2	12-03-1998
		EP 0931065 A2	28-07-1999
		JP 2000517332 T	26-12-2000
WO 9637202 A	28-11-1996	US 5674895 A	07-10-1997
		AU 695194 B2	06-08-1998
		AU 5639296 A	11-12-1996
		AU 718849 B2	20-04-2000
		AU 9052298 A	14-01-1999
		BE 1009462 A3	01-04-1997
		CA 2218714 A1	28-11-1996
		CH 690955 A5	15-03-2001
		DE 19681389 T0	23-04-1998
		FR 2734483 A1	29-11-1996
		GB 2318055 A ,B	15-04-1998
		IT T0960427 A1	21-11-1997
		JP 11505264 T	18-05-1999
		NL 1003185 C2	03-12-1996
		NL 1003185 A1	25-11-1996
		NZ 307116 A	29-03-1999
		US 6124355 A	26-09-2000
		WO 9637202 A1	28-11-1996
		US 6262115 B1	17-07-2001
		US 5840754 A	24-11-1998
		US 2001005728 A1	28-06-2001
		US 5912268 A	15-06-1999
WO 0189473 A	29-11-2001	AU 4638901 A	15-10-2001
		AU 6008901 A	03-12-2001
		WO 0174335 A1	11-10-2001
		WO 0189473 A1	29-11-2001
US 6203817 B1	20-03-2001	NONE	
WO 9967231 A	29-12-1999	IT MI981408 A1	20-12-1999
		AU 4513999 A	10-01-2000
		BR 9911305 A	23-10-2001
		CN 1315945 T	03-10-2001
		WO 9967231 A1	29-12-1999
		EP 1087953 A1	04-04-2001
		HU 0102719 A2	28-12-2001
GB 2330579 A	28-04-1999	FR 2770519 A1	07-05-1999
EP 1092719 A	18-04-2001	BR 0004779 A	29-05-2001
		EP 1092719 A2	18-04-2001
		JP 2001151778 A	05-06-2001
DE 19540642 A	07-05-1997	DE 19540642 A1	07-05-1997
EP 1020190 A	19-07-2000	AU 5597799 A	04-05-2000
		EP 1020190 A2	19-07-2000
		HU 9903732 A2	28-08-2000

INTERNATIONAL SEARCH REPORT

In onal Application No
PCT/EP 01/08734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1020190 A		JP 2000128804 A	09-05-2000
US 5525604 A	11-06-1996	AT 163647 T	15-03-1998
		CA 2130878 A1	27-02-1995
		CN 1109055 A	27-09-1995
		DE 69408750 D1	09-04-1998
		DE 69408750 T2	23-07-1998
		DK 640599 T3	28-09-1998
		EP 0640599 A1	01-03-1995
		ES 2114662 T3	01-06-1998
		JP 7089958 A	04-04-1995
		KR 204433 B1	15-06-1999
US 5436233 A	25-07-1995	AT 208771 T	15-11-2001
		CA 2100626 A1	16-01-1994
		DE 69331122 D1	20-12-2001
		DE 69331122 T2	20-06-2002
		DK 579496 T3	25-02-2002
		EP 0579496 A1	19-01-1994
		ES 2167325 T3	16-05-2002
		JP 2657760 B2	24-09-1997
		JP 6192235 A	12-07-1994
		JP 2923742 B2	26-07-1999
		JP 8099962 A	16-04-1996
		US 5439895 A	08-08-1995
		KR 191416 B1	15-06-1999
WO 9628448 A	19-09-1996	AU 708809 B2	12-08-1999
		AU 5093396 A	02-10-1996
		CA 2211729 A1	19-09-1996
		CZ 9702806 A3	15-04-1998
		EP 0813534 A1	29-12-1997
		HU 9801394 A2	28-10-1998
		JP 11501926 T	16-02-1999
		NO 974150 A	07-11-1997
		NZ 303886 A	25-11-1998
		PL 322452 A1	02-02-1998
		US 5958929 A	28-09-1999
		WO 9628448 A1	19-09-1996
		US 5736548 A	07-04-1998
		ZA 9601948 A	17-09-1996
EP 0943613 A	22-09-1999	AU 4967697 A	10-06-1998
		EP 0943613 A1	22-09-1999
		WO 9822455 A1	28-05-1998
WO 0051988 A	08-09-2000	IT MI990413 A1	04-09-2000
		AU 3158800 A	21-09-2000
		BR 0008582 A	13-02-2002
		CN 1342147 T	27-03-2002
		WO 0051988 A1	08-09-2000
		EP 1154999 A1	21-11-2001